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HOWREY LLP-CA
C/O IP DOCKETING DEPARTMENT
2941 FAIRVIEW PARK DRIVE, SUITE 200
FALLS CHURCH, VA 22042-2924

EXAMINER	
LONG, SCOTT	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,268	KLEINSCHMIDT ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,16-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,16-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 9 March 2009.

Claim Status

Claims 11, 16-18 and 20 are pending. Claims 1-10, 12-15 and 19 are cancelled. Claim 11 is amended. Claims 11, 16-18 and 20 are under current examination.

Priority

This application claims benefit as a 371 of PCT/EP04/006222 (filed 6/9/2004). The application also claims benefit from foreign application EPO 03013169.2 (filed 6/11/2003). The instant application has been granted the benefit date, 11 June 2003, from the application EPO 03013169.2.

RESPONSE TO ARGUMENTS

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 16-18 and 20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Warrington et al. (US2006/0088936, published 27 April 2006) in view of Bartlett et al. (US Patent 6,962,815, issued 8 November 2005) and further in view of

Kaplitt et al. (US Patent, 6,162,796, issued 19 December 2000) and further in view of Wu Xiao (PhD Dissertation 2002, University of Florida) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant has submitted amendments to claim 11 which has changed "delivering to a patient " to " delivering to the heart muscle tissue of a patient " (underlining indicates amendment). Fundamentally, this amendment has not changed the scope of the instant claims, because the specification's examples use and the claims (e.g., claim 20) recite systemic (I.V.) delivery. Therefore, it is the targeting to heart, rather than direct injection of heart which is taking place.

The applicant makes four arguments in traversal of the pending rejection:

1. **Neither reference has disclosed double mutations at positions 484 and 585.** The examiner fully accepts the truth of this statement. However, single mutations at positions 484 and 585 are taught or suggested by the cited art. Furthermore, it was taught that both of these sites involved in heparin binding. Furthermore, the cited art shows that double mutations in the heparin binding site (e.g., R585 and R588) are shown to eliminate heparin binding, known to be related to AAV particle infectivity. Because the particular positions R484 and R585 were suggested by the art as sites which would eliminate heparin binding, and double mutations in the heparin-binding motifs of AAV capsid proteins were shown to eliminate binding, the examiner believes there is sufficient suggestion of the claimed double mutations at positions 484 & 585. In addition, Warrington et al. suggest the nexus between R484

and R585, "R484, which is basic in all five serotypes was tested because of its proximity to R585 and R588, and subsequently proved to be involved in heparin binding" (page 33, parag.0261). Therefore, the examiner finds the applicant's argument unpersuasive.

2. **Neither reference has disclosed the mutations at positions 484 and 585 from R to E.** The examiner fully accepts the truth of this statement. The examiner has proposed that a skilled artisan would understand that altering the amino acids of AAV capsids important for heparin binding function would require changing the from the basic, Arginine, to a neutral or perhaps strongly acidic amino acid, such as Glutamic Acid (E). The applicant suggests "[t]here are more than 15 amino acids that are neutral or acidic. Without hindsight, it is not possible to (i) select E from the 15 non-basic amino acids, (ii) carry out the double mutations at R484 and R585, and then (iii) prove that the R484/R585 double-mutant 'shows a similar loss of cell binding and heparin binding; and was found to be 'even more affected in the infectivity than single mutants." The examiner used the "obvious to try" reasoning now permitted under KSR, in which there were a limited number of known options and possible solutions. In addition, Warrington provides a screening method and some knowledge in the field, regarding infectivity of AAV having double mutations. The examiner describes in detail in the reiterated rejection, below, all of the motivations to combine and the rationale why a skilled artisan might mutate positions 484 and 585 from R to E. Therefore, the examiner finds the applicant's argument unpersuasive.

3. **Neither reference has disclosed delivering AAV-2 vector carrying double mutations to heart muscle.** The applicant further states that wild-type AAV could be detected in liver and heart, while the double mutated AAV was not detectable in the liver, yet was detected in the heart tissue. The applicant is describing an altered tropism of the double mutant AAV. Several of the references (Warrington, Bartlett, and Xiao) teach altered tropism of mutant AAV with reduced binding to heparin receptors. In addition, Kaplitt et al. teach, "AAV naturally infects heart muscle…AAV vectors can yield long-term expression not observed with other systems" (parag.0025) and "the present invention results in gene transfer and expression to a wide area of heart muscle" (parag.0027). Therefore, there is ample suggestion that there would be delivery to the cardiac muscle and that there would be reduced heparin binding in such mutated AAV. Therefore, the examiner finds the applicant's argument unpersuasive.

4. **Unexpected advantages.** The applicant argues "there is not a sufficient rationale to combine" the cited references. This argument has been addressed in arguments 1 and 2. The applicant can review the overall rationale in the reiterated rejection below. The applicant argues the proposed double mutant AAV would not have been predictable. Contrary to the applicant's suggestion, there is a high degree of predictability; the cited art has produced double mutant AAV which abolished heparin binding and has identified the claimed mutations sites as important to heparin binding. This particular knowledge provide a large degree of predictability. Therefore, the examiner finds the applicant's arguments unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 11, 16-18 and 20 under 35 U.S.C. 103(a) as being obvious over Warrington et al. in view of Bartlett et al. and further in view of Kaplitt et al. and further in view of Wu Xiao

The examiner reiterates the pending rejection:

Claims 11, 16-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warrington et al. (US2006/0088936, published 27 April 2006) in view of Bartlett et al. (US Patent 6,962,815, issued 8 November 2005) and further in view of Kaplitt et al. (US Patent, 6,162,796, issued 19 December 2000) and further in view of Wu Xiao (PhD Dissertation 2002, University of Florida).

Claim 11 is directed to a method of gene therapy in a heart muscle tissue of a patient, comprising delivering to the heart muscle tissue of a patient an AAV-2 vector or an AAV particle having a capsid encoded by the AAV-2 vector, wherein the AAV-2 vector carries mutations in a heparin-binding motif of a capsid protein and causes a reduced or eliminated heparin binding function, wherein said mutations are R484E/R585E, wherein amino acids R484 and R5895 belong to different capsid protein subunits.

Warrington et al. teach “recombinant adeno-associated viral (rAAV) vectors having mutations in one or more capsid proteins. Exemplary vectors are provided that have altered affinity for heparin or heparin sulfate" (abstract). Warrington et al. teach rAAV vectors…comprising…R585A …mutation, affinity for heparin sulfate binding by the vector was eliminated.” (page 3, parag.0028) Warrington et al. disclose rAAV comprising identify mutant R484A as having reduced heparin binding (page 8,

parag.0075). Warrington et al. teach delivery of AAV vectors by intravenous administration. . Although, Warrington et al. does not recognize that their vectors will target specifically to cardiac tissue, they do teach that these mutations will alter tropism of the AAV.

While Warrington et al. recognizes the importance of mutations to R484 and R585 for heparin binding of AAV-2 vectors, Warrrington does not specifically recommend mutating them to Glutamic Acid (E). Warrington et al. describe studies of heparin binding based on AAV vectors comprising R484A or R585A. Additionally, Warrington et al. teach double mutants comprising R585A/R588A, suggesting the possibility of double mutant AAV vectors having at least one of the claimed mutations. In addition, Warrington suggests that "conservative double mutant R585K/R588K, and the heparin positive mutant, N587A, was indistinguishable from wild type" in regard to heparin binding motif-related transduction related (page 32, parag.0255). Since both Arginine (R) and Lysine (K) are strongly basic, polar amino acids, a skilled artisan would conclude that substitutions of the important amino acids R585 and R484 with other amino acids besides basic, polar amino acids would be preferable. In further support of this line of thinking, Warrington et al. teach "the determinants of HS-protein interactions suggests that their association is driven mainly by electrostatic attraction between acidic sulfate groups on the polysaccharide and basic R-groups on amino acids in the target protein….It was hypothesized that similar electrostatic interactions would govern HSPG-AAV2 association." (page 29, parag.0242). So, a skilled artisan would understand that altering the amino acids of AAV capsids important for heparin binding function would

require changing the from the basic, Arginine, to a neutral or perhaps strongly acidic amino acid, such as Glutamic Acid (E). Furthermore, Warrington et al. suggest that R484 and R585, being involved in the heparin binding motif, “contribute to a basic patch on one side of each three-fold related spike” (page 33, parag. 0265), indicating how vulnerable this motif would be to disruption by substitution of an alternative acidic amino acid (such as glutamic acid (E) for the critical basic amino acids (arginines) of R484 and R585.

In addition, Warrington et al. suggest the nexus between R484 and R585, “R484, which is basic in all five serotypes was tested because of its proximity to R585 and R588, and subsequently proved to be involved in heparin binding” (page 33, parag.0261). As indicated above, Warrington et al. suggest the idea of using double mutant AAV vectors. Warrington et al. also indicated that "[m]utants that contained substitutions at both positions had even lower infectivity" (page 33, parag.0262), demonstrating the double mutants could be advantageous over single mutations. Warrington et al. suggest that amino acids R484 and R585 belong to different capsid protein subunits, when discussing the position of these amino acids in relation to the atomic structure of AAV2, "residues R585 and R588, which are contributed by one of the peptides in the trimer, are positioned above a linear arrangement of R484, R487, and K532, which are contributed by a second peptide in the trimer. Thus it appears that a heparin binding motif is formed form some combination of these five amino acids using amino acids from two different polypeptides" (page 33, parag. 0265).

Bartlett et al. teach, "Recent research on AAV has therefore involved attempts to modify the viral genome. As the range of cells that AAV will infect is so broad, some researchers have focused on modifying the virus so that it targets specific types of cells for infection. The cellular range or tropism of the virus is determined by the binding of AAV capsid protein(s) to receptor and/or coreceptor proteins expressed on the surface of target cells. Heparin-sulfate proteoglycans (HSPG) is the primary cellular attachment receptor for AAV2." (col.2, lines 11-19). Bartlett et al. further teach, "AAV vectors of the invention that exhibit an altered cellular tropism may differ from wild type in that the natural tropism of AAV may be reduced or abolished" (col.4, lines 41-65). The instant application states, "Mutational analysis of AAV-2 capsid proteins VP1, VP2 and VP3, respectively showed that a group of basic amino acids (arginines 484, 487, 585, 588 and lysine 532; numbering according to the numbering based on VP1 protein id AAC03780.1 NCBI accession No. AF043303) contributes to heparin and HeLa cell binding. These amino acids are positioned in three clusters on the threefold spikes of the AAV-2 capsid." (page 4, 1st parag.). Bartlett et al. further teach amino acids 584 and 588 of VP1 as being important to heparin binding (col.17, lines 1-7 and col.41, line 26). This AAV vector contains at least one mutation to the capsid proteins in amino acid positions 470 to 592, which affects heparin binding. Bartlett et al. teach "The AAV-RGD vectors A588-RGD4C-eGFP and A588-RGD4CGLS were tested for their ability to target gene transfer to the ovarian cell lines as described in Example 9…were able to more efficiently direct gene transfer…compared to wild type AAV vector containing unmodified capsid" (col.19, lines 56-64).

Bartlett et al. do not teach specific delivery of AAV to heart muscle tissue and do not explicitly teach AAV mutants comprising amino acid substitutions R484E and R585E. However, Bartlett et al. do teach the general concept of AAV-2 vectors comprising double mutations of amino acids important for heparin binding.

Kaplitt et al. teach, “AAV naturally infects heart muscle…AAV vectors can yield long-term expression not observed with other systems” (parag.0025) and “the present invention results in gene transfer and expression to a wide area of heart muscle” (parag.0027).

Kaplitt et al. do not teach the specific mutations of capsid proteins and its corresponding effect on heparin-sulfate binding proteins as required by the instant claims.

However, Wu Xiao et al. teach “to increase the targeting of rAAV vectors…1) reducing the natural tropism of AAV, and 2) increasing the tissue specificity of AAV…[have been attempted by] groups [of researchers who] have been trying to locate sites of AAV capsid for receptor binding and the sites exposed on the surface of the capsid by doing extensive capsid mutagenesis experiments" (page 14, lines 6-10). Wu Xiao also teaches “double mutants at amino acid 585 and 588 of AAV capsid protein abolish its heparin binding activity” (page 14, lines 19-20).

Claims 16-18 are directed to further limitations of the claims, wherein the AAV capsid proteins are VP1 (claim 17); VP1, VP2, or VP3 (claim 16); number of amino acid position is according to VP1 (claim 18). Claim 20 is directed to system delivery of the AAV. All of the limitations of claims 16-18 and 20 are taught by the cited references.

It would have been obvious to one skilled in the art to use an AAV vector having mutations to the capsid proteins in amino acid positions 484 and 585, which affects heparin binding in a method of gene therapy to heart muscle tissue.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (mutations to AAV-2 capsid protein at positions 484 and 585; and AAV having a specificity for heart muscle tissue) are taught by Warrington, Bartlett, Kaplitt, and Wu Xiao. Wu Xiao, in particular, teaches that mutations of capsid proteins are capable of limiting the range of cellular targeting by AAV.

In addition, the claimed invention is obvious because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and commonsense." The prior art teaches the need in the art to solve the problem of optimally "disrupting the heparin binding site on AAV-2 vectors used for gene delivery" and further identifies a number of predictable potential solutions for making mutations to the heparin binding motif of AAV-2, including mutating both amino acid positions R484 and R585. The possible number of alternative amino acids is limited and furthermore, the prior art clearly recommends against a strongly basic amino acid as the substitution for Arginine. All of the potential solutions would have been known by

a skilled artisan. One of ordinary skill in the art could have pursued the known potential options (of substituting non-basic amino acids for the arginines of R484 and R585) with a reasonable expectation of success. Therefore, it would be predictably obvious to use alternative amino acids when creating the R484E/R585E AAV-2 double mutant.

Therefore the methods as taught by Warrington et al., in view of Bartlett et al. and further in view of Kaplitt et al. and further in view of Wu Xiao would have been *prima facie* obvious over the method of the instant application.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Patent Examiner, Art Unit 1633

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633